Imaging the prenatal brain in congenital heart defects

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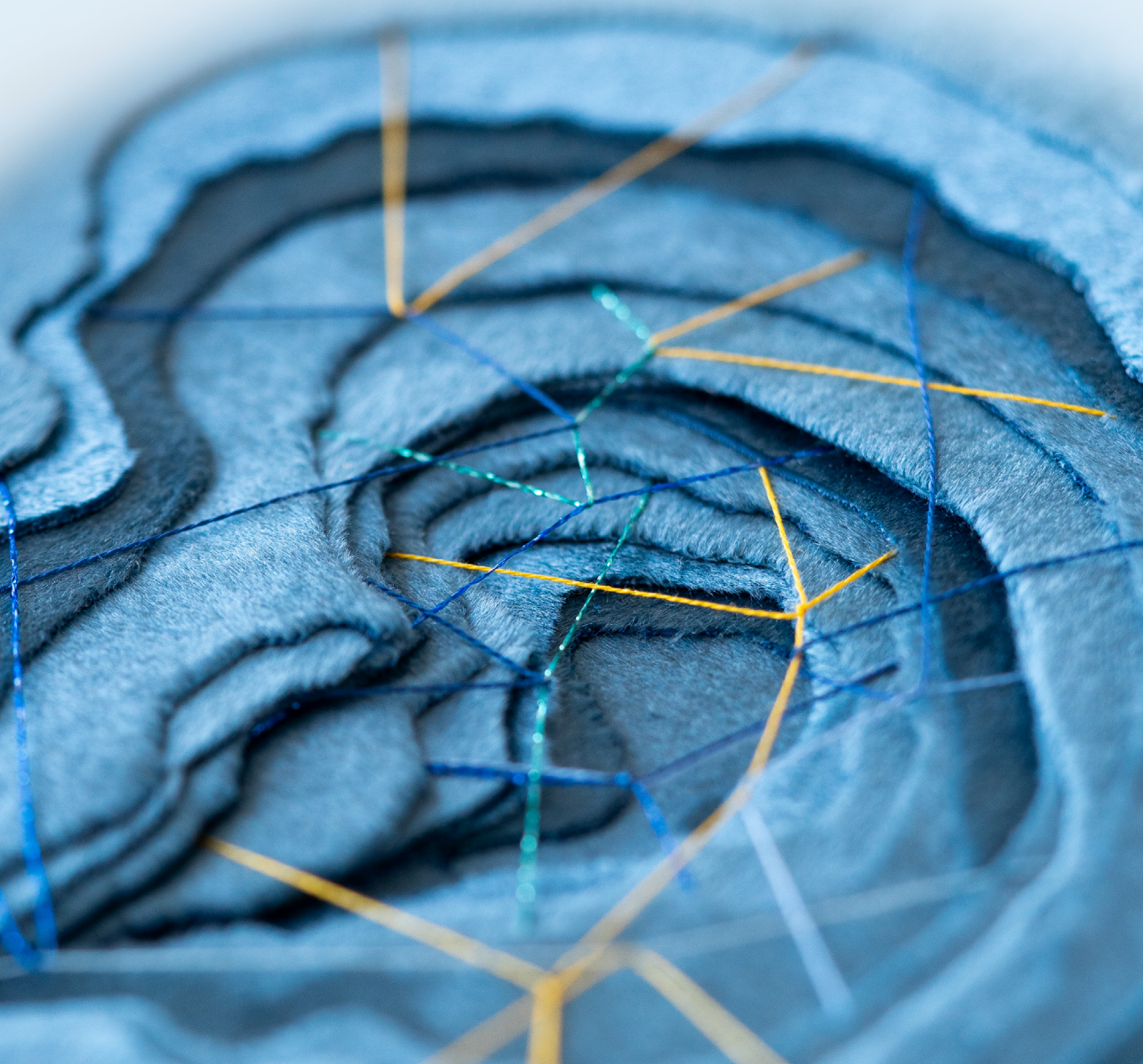
CHAPTER

1

Introduction and outline



INTRODUCTION

Congenital heart defects (CHD) are the most prevalent congenital abnormalities. CHD has been defined as 'a gross structural abnormality of the heart or intra-thoracic great vessels that is actually or possibly of functional significance'[1]. About 25-30% of children that are diagnosed with CHD require surgery in the first year of life[2]. A prenatal diagnosis of CHD leads to optimized neonatal care, and is thought to be correlated to improved long-term outcome.[3] For some defects, interventions are required directly after birth, for example the administration of prostaglandins to keep the ductus arteriosus open, or a Rashkind procedure to sustain flow through the oval foramen.

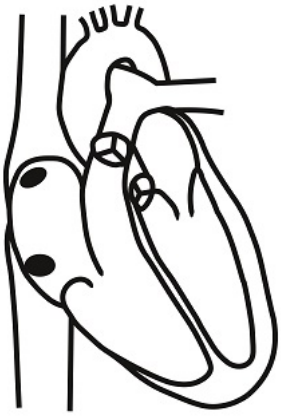
Thus, the aim of a screening program is to strive for high detection rates to optimize care for children with (cardiac) congenital defects. Previous studies in the Netherlands have shown a detection rate of 95% in defects that present with an abnormal aspect of the four-chamber view[4]. Defects that affect the out-flow tracts of the heart (conotruncal abnormalities) have a significantly lower detection percentages[5]. Detection rates differ significantly, even in developed countries. However, the detection rates in the Netherlands were already relatively good, and are rising in other countries as well[6].

PART I
Prenatal detection of CHD

A prenatal diagnosis affects survival in neonates with critical CHD. For example, prenatally detected neonates with transposition of the great arteries (TGA) showed no mortality as compared to 12% preoperative mortality in undiagnosed cases[7]. Also, a timely diagnosis reduces morbidity such as brain and kidney damage, as a child can receive optimal peripartum care[8]. In non-critical CHD, like the majority of tetralogy of Fallot (TOF)) cases, a prenatal diagnosis does not prevent immediate postnatal deterioration, but gives the opportunity to diagnose genetic syndromes before birth. Defects like TOF carry a relatively high risk for a genetic syndrome, which may significantly alter the long-term outcome of the child. If diagnosed in time, this may enable reproductive choices for the parents.

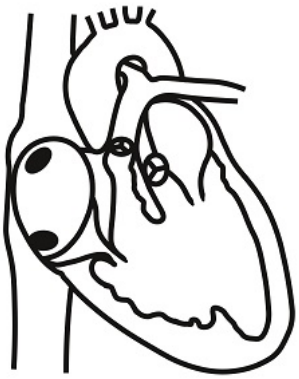
Both TGA and Fallot are examples of CHD that usually present with a normal four-chamber view on ultrasound and detection of these abnormalities is perceived as more difficult by ultrasonographers. Recently, a study by van Nisselrooij et al[9] showed no significant differences in patient-related factors such as fetal position, obstetric history, maternal age or gestational age at examination when images of missed CHD cases were compared to detected cases. Furthermore, this study

showed that cardiac examinations appeared of better quality when performed by sonographers who carried out a greater number of SAS per year. Sonographers that missed diagnoses had all passed quality assessment, however, 25% of sonographers did not obtain or save all cardiac planes, indicating that they either did not obtain and save all cardiac planes in a structured manner or accepted technically incorrect planes. A diagnostic clue in CHDs with a normal four-chamber view is the inability to produce a normal three vessel view (3vv) in these cases. In this thesis, the effect of adding this additional plane to the screening program on the detection of TGA and Fallot is examined. As the 3vv was added in 2012, we could compare the detection rates of TGA and Fallot before and after the introduction of this plane.
Part II of this thesis covers the prenatal neurodevelopment in CHD. Since long term neurodevelopmental outcome is strongly correlated to prenatal detection, this thesis starts with an article on improving prenatal detection.



Normal heart

Transposition of the great arteries



Tetralogy of Fallot

PART II
Neurodevelopment in congenital heart defects

The first open heart surgery for a congenital heart defect was performed at Johns Hopkins University, United States, in 1944. As children who underwent cardiac surgery increasingly survive into adulthood (the oldest living persons with an arterial switch operation are now in their forties), this allows for long-term follow-up studies. Adolescents living with CHD are known to have a high morbidity rate, with problems such as neurocognitive impairment, despite advances in (peri) operative care. Behavioral problems like ADHD, lower IQ and impaired executive functions are more common in this group. Until recent years these problems were attributed

to the detrimental effects of cardiopulmonary bypass and low cardiac output and low oxygen saturations in the perioperative period. Logically, children with cardiac defects in the severe end of the spectrum, such as hypoplastic left heart syndrome, are prone to worse neurodevelopmental outcome, since these children undergo more complex and often multiple operations. A study by Marino et al. published in Circulation in 2012, showed that 23 percent of children with severe CHD had behavioral and cognitive impairments and around 5% had problems in everyday life[10]. More recently, in addition to other etiological factors, a prenatal origin of delays in neurodevelopmental has been suggested. Studies performed in neonates with transposition of the great arteries and single ventricle pathology showed significantly higher rates of gray and white matter brain damage on pre ***and*** postoperative MRI's[11]. Mild microcephaly prior to surgery was seen in 25-36% of neonates with CHD, and 40-55% present with signs of neurological impairment (abnormal tonus, absent suck-reflex)[12]. Prenatal studies performed in fetuses with CHD showed signs of significant delayed head circumference (HC) growth and a lower resistance in the cerebral artery, known as brainsparing, without evident growth restriction[13, 14]. Studies addressing prenatal cortical development in this CHD fetuses using ultrasound and MRI showed severe delays up to 3 weeks compared to control fetuses. The hypothesis that neurodevelopmental impairment originates in fetal life, does not completely fit with the long term outcome of these children as most children present with minor behavioral problems. This thesis elaborates on the question: Do fetuses with CHD really show signs of delayed cortical maturation on ultrasound, and if so, what is the extend of the delay and are some types of CHD more prone to delayed maturation than others?

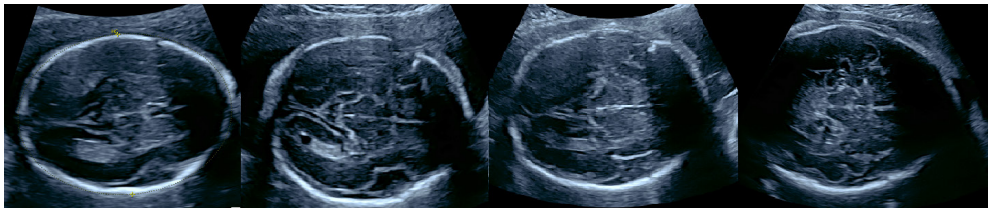


Figure 1 *The Sylvian fissure progresses from a shallow indentation (left picture, 20 weeks), to an angular shape (second picture, 24 weeks), to <50 opercularisation (third picture, 28 weeks) and ≥50% opercularisation (right picture, 32 weeks).*

Comparing cortical development in congenital heart defect cases and controls using ultrasound and advanced imaging analysis.

Fetal Cerebral Cortex

The maturation of the cerebral cortex is very rapid in fetal life and can be easily visualized with ultrasound and MRI, thus, making it a suitable parameter to study development. Moreover, it is known from studies in asphyctic neonates that periods of hypoxia can damage the cerebral cortex, leading to poor neurodevelopment later in life[15]. This has led to the concept that the hemodynamics in fetal CHD may result in altered flow/oxygenation of the fetal brain which in turn lead to different maturation patterns. Previously mentioned studies in prenatal cortical development present however, with forms of selection bias: for example, severe, non-isolated CHD cases (for example HLHS) are included more often, and only a single MRI acquisition in the third trimester was obtained. These results do not reflect cortical development in the whole group of CHD, and therefore extrapolation is difficult. The actual effect of different types of CHD on prenatal cortical development, and the extent of the delay in brain maturation is currently not known. To answer this question, a number of fetuses and healthy controls was sequentially examined with ultrasound and the maturation of the cortex was scored blinded afterwards. Since manual scoring of images is a time-consuming method and is also prone to human error, we have sought the aid of novel imaging analysis techniques. The algorithm that is presented in this thesis is a form of automated image analysis that was used to automatically analyse our imaging data.

Automated image analysis

Artificial intelligence (AI) is the technology that uses data and algorithms and has the ability to learn and adapt from input and observations. This type of AI is called deep machine learning, which means that an algorithm is trained with images that are labelled 'normal' and 'abnormal' and can subsequently recognize abnormal situations. AI is already used in daily life, for example in face and speech recognition on our smartphones. In healthcare an enormous amount of digital data is produced and daily practice relies heavily on human observations for triage, diagnosis and management. Thus, the implementation of AI, especially for specialties that produce medical imaging, seems to be a logical next step to aid physicians. A recent publication by Drukker et al.[16], describes different applications in obstetric medicine that are currently being researched, such as prediction of fetal lung maturity, pregnancy dating in advanced gestation or the prediction of shoulder dystocia. Most of these innovations use deep learning to detect patterns in observations, which were also used to program the algorithm that was applied in this thesis. It uses graytones to asses cortical development and is thereafter expressed in gestational age. This algorithm has been originally designed for developing countries, to estimate gestational age in pregnancies that did not receive accurate pregnancy dating. In

our study cohort, the algorithm is applied to CHD and control fetuses to assess brain maturation and thus conclude on prenatal delays in neurodevelopment.

OUTLINE OF THIS THESIS

Widespread use of ultrasonography has greatly evolved prenatal medicine over the past decades. Both the prenatal detection of cardiac defects and the diagnosis of prenatal brain development have significantly improved. In this thesis, the impact of screening protocols are studied on the prenatal detection of cardiac defects. Furthermore, to explore the hypothesis of altered neurodevelopment, prenatal brain development was studied in a large number of congenital heart defect cases, and analysed both manually and by using automated imaging analysis.

Part one describes the effect of the introduction of the 3vv in the standard anomaly scan protocol in 2012. The three-vessel is an instrument to increase the detection of outflow tract anomalies, which are known to have lower detection rates than CHD that present with an abnormal four-chamber view. The detection rates of transposition of the great arteries and tetralogy of Fallot were compared before and after the introduction of the three-vessel view.

In **part two** of this thesis, the prenatal neurodevelopment in congenital heart defect cases is assessed with two and three-dimensional ultrasound. Artificial intelligence has been used to estimate the magnitude of the difference in brain development.
Chapter 3 describes the results of a systematic review and meta-analysis of prenatal brain development in CHD cases. We have included all studies concerning US and MRI in isolated CHD published between January 1990 - October 2015. Multiple parameters such as HC-growth, cerebral and umbilical blood-flows, structural brain anomalies and neurological follow-up were compared to each other. In **chapter 4,** we assessed the feasibility of advanced neurosonography in a limited time frame, we have scored the visibility of cerebral structures in CHD and control cases.
In **chapter 5,** CHD-cases are compared to control fetuses to assess differences in cortical development using manual, blinded scoring of the cerebral cortex using the scoring scheme as published by Pistorius et al[17].
A novel approach to examining 3D ultrasound volumes using a brain-age estimation algorithm is presented in **chapter 6 and 7**. **Chapter 6** presents the brain maturation scores of all isolated CHD-cases compared to controls. In **chapter 7,** the brain age of CHD cases pooled according to their anatomic features are presented.
In **Chapter 8** a general discussion of the combined results is presented. Finally, **Chapter 9** shows a general summary.

Ethical aspects

The HAND-study has included both CHD-fetuses and healthy control fetuses. The local ethics committee has approved the HAND-study protocol on March 17, 2014. The CHD-fetuses were exempt from WMO, this allowed CHD fetuses to be scanned under routine care circumstances. Permission for the HAND control group of healthy fetuses was obtained by parents informed consent.

References

1 Mitchell SC, Sellmann AH, Westphal MC, et al. **Etiologic correlates in a study of congenital heart disease in 56,109 births.** The American journal of cardiology 1971;286:653-7.

2 Pasupathy D, Denbow ML, Rutherford MA, et al. **The Combined Use of Ultrasound and Fetal Magnetic Resonance Imaging for a Comprehensive Fetal Neurological Assessment in Fetal Congenital Cardiac Defects**: Scientific Impact Paper No. 60. BJOG 2019;1267:e142-e51.

3 Bonnet D. **Impacts of prenatal diagnosis of congenital heart diseases on outcomes.** Transl Pediatr 2021;108:2241-9.

4 van Velzen CL, Ket JCF, van de Ven PM, et al. S**ystematic review and meta-analysis of the performance of second-trimester screening for prenatal detection of congenital heart defects.** Int J Gynaecol Obstet 2018;1402:137-45.

5 van Velzen CL, Clur SA, Rijlaarsdam ME, et al. P**renatal detection of congenital heart disease--results of a national screening programme.** BJOG 2016;1233:400-7.

6 Aldridge N, Pandya P, Rankin J, et al. **Detection rates of a national fetal anomaly screening programme: A national cohort study.** BJOG 2022.

7 van Velzen CL, Haak MC, Reijnders G, et al. **Prenatal detection of transposition of the great arteries reduces mortality and morbidity.** Ultrasound Obstet Gynecol 2015;453:320-5.

8 Calderon J, Angeard N, Moutier S, et al. **Impact of prenatal diagnosis on neurocognitive outcomes in children with transposition of the great arteries.** The Journal of pediatrics 2012;1611:94-8 e1.

9 van Nisselrooij AEL, Teunissen AKK, Clur SA, et al. **Why are congenital heart defects being missed?** Ultrasound Obstet Gynecol 2019.

10 Marino BS, Lipkin PH, Newburger JW, et al. **Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association.** Circulation 2012;1269:1143-72.

11 Peyvandi S, Donofrio MT. **Circulatory Changes and Cerebral Blood Flow and Oxygenation During Transition in Newborns With Congenital Heart Disease.** Semin Pediatr Neurol 2018;28:38-47.

12 Majnemer A, Limperopoulos C, Shevell MI, et al. **A new look at outcomes of infants with congenital heart disease.** Pediatric neurology 2009;403:197-204.

13 Modena A, Horan C, Visintine J, et al. F**etuses with congenital heart disease demonstrate signs of decreased cerebral impedance.** Am J Obstet Gynecol 2006;1953:706-10.

14 Szwast A, Tian Z, McCann M, et al. **Comparative analysis of cerebrovascular resistance in fetuses with single-ventricle congenital heart disease.** Ultrasound Obstet Gynecol 2012;401:62-7.

15 de Vries LS, Groenendaal F. **Patterns of neonatal hypoxic-ischaemic brain injury.** Neuroradiology 2010;526:555-66.

16 Drukker L, Noble JA, Papageorghiou AT. I**ntroduction to artificial intelligence in ultrasound imaging in obstetrics and gynecology.** Ultrasound Obstet Gynecol 2020;564:498-505.

17 Pistorius LR, Stoutenbeek P, Groenendaal F, et al. **Grade and symmetry of normal fetal cortical development: a longitudinal two- and three-dimensional ultrasound study.** Ultrasound Obstet Gynecol 2010;366:700-8.